IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application of
HARBIGE et al
Serial No. 10/756,761
Filed: January 14, 2004

Conf. No.: 1504
Atty. Ref.: LCM-604-706
TC/A.U.: 1627
Examiner: Kantamneni, Shobha

For: TREATMENT OF NEURODEGENERATIVE CONDITIONS

* *

March 14, 2011

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Sir:

Appellant hereby **appeals** to the Board of Patent Appeals and Interferences from the last decision of the Examiner.

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(I) REAL PARTY IN INTEREST

The real party in interest is BTG International, Ltd., a corporation of the United Kingdom.

(II) RELATED APPEALS AND INTERFERENCES

The appellant, the undersigned, and the real party in interest/assignee are not aware of any related appeals, interferences, or judicial proceedings (past or present), which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

(III) STATUS OF CLAIMS

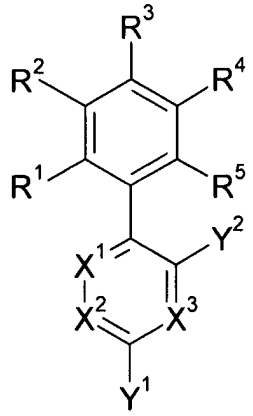
Claims 1-3, 6-11, 14, 15 and 16 are pending and have been rejected. Claims 4, 5, 12 and 13 are canceled. No claims have been substantively allowed. Claims 1-3, 6-11, 14, 15 and 16 are appealed.

(IV) STATUS OF AMENDMENTS

No amendments have been filed since the date of the last rejection which was the second rejection of the claims under appeal.

(V) SUMMARY OF CLAIMED SUBJECT MATTER

The invention as claimed in claim 1 relates to a method of treating a patient in need of therapy for multiple sclerosis by administering to that patient a therapeutically effective dose between 500mg/day and 700mg/day of a compound of formula I:



wherein R^1, R^2, R^3, R^4 and R^5 are independently selected from the group consisting of hydrogen, trihaloalkyl and halo substituents;

X^1, X^2 and X^3 are independently selected from the group consisting of CH, CCH_2F, CCF_3, CO alkyl, CCH_3, and nitrogen , with at least two of X^1, X^2 and X^3 being nitrogen; and Y^1 and Y^2 are independently selected from the group consisting of hydrogen, NH_2 and tertiary amino groups wherein the tertiary amino groups are selected from -1-piperazinyl and 4-alkyl-1-piperazinyl (specification, page 3, line 20 to page 4, line 2; page 4, lines 4-8; page 4, lines 15 and 16; page 5, line 13).

(VI) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds of rejection to be reviewed on appeal are:

1. The obviousness rejection of claims 1-3, 6-9, 11 and 16 over Bountra *et al.* (Bountra).

2. The obviousness rejection of claims 10, 14 and 15 over Bountra.

3. The obviousness rejection of claims 1-3, 6-9, 11 and 15 over Lunardi *et al.* (Lunardi).

(VII) ARGUMENT

The invention as claimed in claim 1 is directed to a method of treating a patient in need of therapy for multiple sclerosis (MS). The method comprises administering to that patient a therapeutically effective dose between 500mg/day and 700mg/day of a compound of formula I wherein R^1, R^2, R^3, R^4 and R^5 are independently selected from hydrogen, trihaloalkyl and halo substituents; X^1, X^2 and X^3 are independently selected from CH, CCH_2F, CCF_3, CO alkyl, CCH_3, and nitrogen, with at least two of X^1, X^2 and X^3 being nitrogen; and Y^1 and Y^2 are independently selected from hydrogen, NH_2 and tertiary amino groups wherein the tertiary amino groups are selected from -1-piperazinyl and 4-alkyl-1-piperazinyl.

Bountra contains no disclosure or suggestion of the method as claimed. Bountra proposes that sodium channel antagonists may be used to treat multiple sclerosis but by a proposed mechanism of preventing neuronal apoptosis. This is irrelevant to multiple sclerosis (MS), because it is well known in the art that this mechanism is not significant in that disease. Moreover, Bountra contains no disclosure or suggestion of the claimed range of 500mg/day and 700mg/day.

The Action mailed October 13, 2010 (page 3, lines 3-6) refers to page 10, lines 1-8 of Bountra. However, that passage merely says that, for different sodium channel blockers, the physician should take into account the age and condition of the patient. In fact, this is what the physicians did in Lunardi (discussed below) in treating multiple sclerosis patients 16-20 with significantly **lower** doses of lamotrigine (i.e., 125 mg/day) than other patients (max 400mg/day). Thus, Bountra urges the physician to take account

of the patient's condition (multiple sclerosis) and to use a **lower** dose accordingly. Bountra, therefore, leads **away** from the presently claimed method which administers higher dosages in the range of 500mg/day and 700mg/day.

The Action (page 3, line 1) also points to claim 7 of Bountra as a disclosure that sodium channel blockers may be used to treat multiple sclerosis. However, in this regard, attention is again directed to Ramsaransing, *et al.* (of record) which indicates that carbamazepine, a sodium channel blocker, makes multiple sclerosis worse. For this further reason, one of ordinary skill, as of the filing date of the present case, would not have been motivated to arrive at the presently claimed method based on Bountra.

Bountra does not give rise to a *prima facie* case of obviousness. Reversal of the obviousness rejection of claims 1-3, 6-9, 11 and 16 over Bountra and reversal of the obviousness rejection of claims 10, 14 and 15 over Bountra are respectfully requested.

Referring to the obviousness rejection of claims 1-3, 6-9, 11 and 15 over Lunardi, that reference states that all of the patients had been on carbamazepine at 200 to 1500 mg/day prior to lamotrigine treatment, but that this treatment had been stopped due to serious side effects. In contrast, Appellants have discovered, surprisingly, that the dosage may be increased to avoid adverse effects (specification, paragraph [0023]). These adverse effects include common occurrence of skin rash (Guberman *et al.*, Epilepsia (1999) 40(7): 985-991, page 990 Table 3 (of record) where a maintenance dose of 200-400mg is used, and Wong *et al.* (1999) Ann. Pharmacotherapy 33:1037-1042 (of record)). These papers are directed to the use of lamotrigine in regard to epilepsy, where a relatively high dose is employed as compared with other conditions. Guberman *et al.*

and Wong *et al.* illustrate why a physician, in light of Bountra's disclosure to take note of the patient's condition, would not have been motivated, as of the filing date of the present application, to use increased doses of lamotrigine.

In further support of the non-obviousness of the claimed dosage, attention is directed to Exhibit 1 (Rule 132 declaration executed by Dr. Jackie Palace (the Palace declaration)) and to Exhibit 2 (Rule 132 declaration executed by Professor Giovannoni (the Giovannoni declaration)). In the Palace declaration, Dr. Palace (a physician having extensive knowledge and experience of multiple sclerosis) declares that she does not agree that patients should be prescribed lamotrigine at doses as high as 900mg. Dr. Palace bases this statement on her review of highest tolerated doses employed in a lamotrigine trial in secondary progressive MS, where the highest tolerated dose was 300mg (average only 78mg) in this trial population. The Palace declaration observes that the maximum dose in that trial was 400mg which, Dr. Palace notes, was the maximum dose in the Lunardi study.

Further papers (copies of record) which evidence the exercise of physician's judgment in use of **reduced** amounts of lamotrigine in treatment of multiple sclerosis are:

Leandri *et al.* (2000) J. Neurol 247:556-558 teaches doses of 25mg up to a maximum of 400mg/day;

Solaro *et al.* (2005) Neurol Sci 25: 307-310 uses 75mg/day to 400mg/day;

Silver *et al.* (2007) Journal of Pain and Symptom Management 34(4): 446-454 uses 200mg/day, 300mg/day and 400mg/day.Breur et al (2007) Clinical Therapeutics 29(9):2022-2030 teaches use of 400mg/day;

Titlie *et al.* (2008) Bratisl Lek Listy 109(9): 421-424 teaches doses of 200mg/day-250mg/day (in post stroke pain).

In the Giovannoni declaration, Professor Giovannoni observes that, prior to the present invention, the recommended daily maximum dosage of lamotrigine (LTG) in the treatment of MS was 400mg daily. Professor Giovannoni notes (paragraph 5) that Lunardi and colleagues treated 15 patients with trigeminal pain with LTG of which 5 patients had MS (patients 16-20). Of the five patients with MS, the highest dose used was 200mg/day (patient 17).

The Action asserts that a physician treating MS patients would have considered Bountra and would have taken at face value the statement at page 10, lines 3-7 of Bountra, in regard to dosage levels of LTG, that:

> "A suitable dose is for example 0.1 mg/kg to 30 mg/kg body weight per day calculated as the free base, for example 3 mg/kg to 15 mg/kg. A suitable dose for an adult human is for example in the range of 200mg to 900 mg per day"

In response, Professor Giovannoni declares that, in his opinion, at the time of the present invention, an experienced neurologist in this art such as himself would not have contemplated administering LTG to a patient suffering from MS in dosage levels higher than the recommended maximum of 400mg daily. Professor Giovannoni's reasoning (paragraph 8) is that LTG is neuroprotective in animal models of global and focal ischaemia *in vivo* at doses of 20mg/kg and above, i.e., greater than 4X the anticonvulsant dose in rats (although the ED50 is 2mg/kg, the rat anticonvulsant ED95 is approximately 5mg/kg. Professor Giovannoni further states (paragraph 9) that in rat middle cerebral

artery occlusion (MCAO) model studies published by Smith and Meldrum in 1995 (*Cerebral protective effect of lamotrigine after focal ischemia in rats,* 1995, Stroke:26, 117-122), LTG is only neuroprotective in this model of focal ischemia over a narrow dose range, and that only a dose of 20mg/kg IV significantly reduced neurological scores.

Professor Giovannoni (paragraph 10) notes that doses of LTG (10-50mg/kg) higher than anticonvulsant doses have been used in other studies of global ischemia to achieve neuroprotection in gerbil, rat and pig (see *Lamotrigine: Mechanisms of Action.* Leach, Randall, Stefani and Hainsworth, 2002, In: Antiepileptic Drugs, 5th edition, Eds. Levy, Mattson, Meldrum, Perucca), and that the minimum effective LTG concentration to block white matter ischaemia *in vitro* is 100uM (*Mechanisms of ischaemic damage to central white matter axons: a quantitative histological analysis using rat optic nerve,* Garthwaite *et al.*, Neuroscience, 1999, 94:1219-1230). Professor Giovannoni declares that a usual adult maintenance dose for LTG monotherapy of 100-200mg daily with plasma concentrations around 2-4ug/ml (8-16uM) is far lower than concentrations of LTG to reduce white matter axonopathy.

In paragraph 12, the Giovannoni declaration states that doses of LTG lower than 400mg per day have been used to treat central pain in patients with MS, and that in the paper by Leandri and colleagues (*Lamotrigine in trigeminal neuralgia secondary to multiple sclerosis,* Leandri *et al.*, 2000. iNeurol. 247:556-558, of record), doses of 25mg daily to a maximum of 400mg daily were used. In paragraph 13, Professor Giovannoni states that pain due to trigeminal neuralgia in patients with MS is usually due to an inflammatory plaque in the root entry zone of the trigeminal nerve and is typically

responsive to anti-convulsant medications within the recommended dose ranges, including that for LTG (<400mg per day), and that the indication in this context is for trigeminal neuralgia or pain and **not** neuroprotection, which was not investigated in these studies. Professor Giovannoni further observes that doses that work against central pain syndromes appear to be similar to typical anti-convulsant doses and are typically lower than doses employed for neuroprotection.

In paragraph 16, Professor Giovannoni concludes that, in light of the published facts prior to the present invention and the subsequent US patent filing in 2004, it would not have been obvious to him, or any other neurologist with skill in the art of administering LTG, that doses higher than the recommended maximum of 400mg daily could be effective to modify the course of the progressive pathology of MS to the extent exhibited in the present patent application.

Based on the above, and Exhibits 1 and 2, it is clear that physicians, post-Bountra, would have interpreted suitable doses as **400mg/day or less**. Neither Bountra nor Lunardi suggests treatment of multiple sclerosis using the claimed dosage level of between 500mg/day and 700mg/day. Thus, taking Bountra alone (or in combination with Lunardi), the physician would **not** have been motivated to arrive at the presently claimed dosage of between 500mg/day and 700mg/day, and would have acted to **reduce** the dosage in the case of multiple sclerosis patients based on the state of the art.

Reversal of the outstanding obviousness rejections is respectfully requested.

CONCLUSION

In conclusion, it is believed that the application is in clear condition for allowance. Early reversal of the outstanding rejections and passage of the subject application to issue are earnestly solicited.

Respectfully submitted,

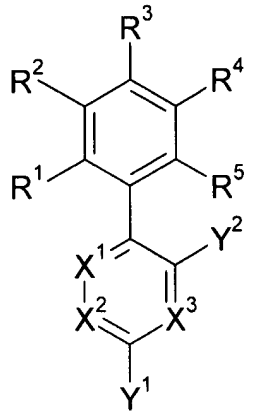
NIXON & VANDERHYE P.C.

By: /Leonard C. Mitchard/
Leonard C. Mitchard
Reg. No. 29,009

LCM:lff
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100

(VIII) CLAIMS APPENDIX

1. A method of treating a patient in need of therapy for multiple sclerosis comprising administering to that patient a therapeutically effective dose between 500mg/day and 700mg/day of a compound of formula I



wherein R^1, R^2, R^3, R^4 and R^5 are independently selected from the group consisting of hydrogen, trihaloalkyl and halo substituents;

X^1, X^2 and X^3 are independently selected from the group consisting of CH, CCH_2F, CCF_3, CO alkyl, CCH_3, and nitrogen , with at least two of X^1, X^2 and X^3 being nitrogen; and Y^1 and Y^2 are independently selected from the group consisting of hydrogen, NH_2 and tertiary amino groups wherein the tertiary amino groups are selected from -1-piperazinyl and 4-alkyl-1-piperazinyl.

2. A method as claimed in Claim 1 wherein R^1 to R^5 are independently selected from hydrogen and chloro, with two or three of R^1 to R^5 being chloro.

3. A method as claimed in Claim 1 wherein X^1, X^2 and X^3 are nitrogen.

4-5 (cancelled).

6. A method as claimed in Claim 1 wherein Y^1 is selected from $-NH_2$, -1-piperazinyl and 4-alkyl-1-piperazinyl and Y^2 is $-NH_2$.

7. A method as claimed in Claim 1 wherein the compound of formula 1 is selected from the group consisting of Lamotrigine: 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, Sipatrigine: 4-amino-2-(4-methyl-1-piperazinyl)-5-(2,3,5-trichlorophenyl)-pyrimidine, 2,4-diamino-5-(2,3-dichlorophenyl)-6-(fluoromethylpyrimidine), R-(-)-2,4-diamino-6-(fluoromethyl)-5-(2,3,5-trichlorophenyl)-pyrimidine, 4-amino-2-(1-piperazinyl)-5-(2,3,5-trichlorophenyl)-pyrimidine (active Sipatrigine metabolite), 4-amino-2-(4-methyl-1-piperazinyl)-5-(2,3,5-trichlorophenyl)-6-trifluoromethylpyrimidine, 2,4-diamino-5-(2,3,5-trichlorophenyl)-trifluoromethylpyrimidine, 2,4-diamino-5-(2,3,5-trichlorophenyl)-6-methoxymethylpyrimidine, 4-amino-6-methyl-2-(4-methyl-1-piperazinyl)-5-(2,3,5-trichlorophenyl)-pyrimidine, 4-amino-2-(4-propyl-1-piperazinyl)-5-(2,3,5-trichlorophenyl)-pyrimidine and 2,4-diamino-5-(2,3,5-trichlorophenyl)-pyrimidine.

8. A method as claimed in Claim 1 wherein the therapy results in reduction of one or more of incidence of relapse, spasticity and fatigue.

9. A method as claimed in Claim 1 wherein the therapy stabilises the patients Expanded Disability Status Score (EDSS), thus halting progress of the disease.

10. A method as claimed in Claim 1 wherein the compound of formula 1 is administered during periods of remission, as well as during relapse, such that the occurrence of relapse is reduced.

11. A method as claimed in Claim 1 wherein the compound of formula I is given at a dose sufficient to reduce spasticity or daytime fatigue.

12-13 (cancelled).

14. A method as claimed in Claim 1 wherein the compound of formula 1 is administered at a dose of about 600mg/day.

15. A method as claimed in Claim 1 wherein the compound is administered in an escalating dosing regime, starting at 100mg/day or less and escalating to the maximum treatment dose of between 500mg/day and 700mg/day over a period of 1 to 10 weeks.

16. A method as claimed in Claim 1, wherein alkyl is methyl, ethyl or propyl.

(IX) EVIDENCE APPENDIX

Exhibit 1: Rule 132 declaration of Dr. Jackie Palace (the Palace declaration) (acknowledged and discussed in the Official Action mailed October 13, 2010);

Exhibit 2: Rule 132 declaration of Professor Giovannoni (the Giovannoni declaration) (acknowledged and discussed in the Official Action mailed October 13, 2010).

(X) RELATED PROCEEDINGS APPENDIX

None.

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HARBIGE et al — Atty. Ref.: 604-706; Confirmation No. 1504

Appl. No. 10/756,761 — TC/A.U. 1627

Filed: January 14, 2004 — Examiner: Kantamneni, Shobha

For: TREATMENT OF NEURODEGENERATIVE CONDITIONS

* * * * * * * * * * * *

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION

I, Jacqueline Palace, hereby declare and state that:

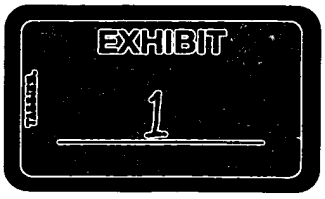
1. I am a consultant neurologist and honorary senior lecturer, Radcliffe Hospitals Trust, Oxford, UK.

2. I specialise in multiple sclerosis (MS) (treatment and research studies).

3. I have reviewed Lunardi *et al.*, Neurology, Vol. 48(6), 1997, pp1714-1717, and the Bountra *et al.* patent application (WO0061231).

4. I understand that the assertion is made that a physician treating MS patients would consider Bountra's statement on page 10, lines 3-7 of Bountra *et al.* that:

> "A suitable dose is for example 0.1 mg/kg to 30 mg/kg body weight per day calculated as the free base, for example 3 mg/kg to 15 mg/kg. A suitable dose for an adult human is for example in the range of 200mg to 900 mg per day."



5. As a physician having extensive knowledge and experience of MS, I do not agree that patients should be prescribed lamotrigine at doses as high as 900 mg. I base this statement on my review of the doses tolerated in Dr Kapoor's recent lamotrigine trial in secondary progressive MS, where the highest tolerated dose was 300 mg (average only 78 mg) in this population. Indeed, the protocol stated a maximum dose of 400 mg, and I note that this was the maximum dose in the Lunardi study.

I declare that all statements herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Jackie Palace

23 3 2010

Date

Barts and The London
School of Medicine and Dentistry

Institute of Cell and Molecular Science
Neuroscience Centre
Barts and The London School of Medicine and Dentistry

Postal Address: Department of Neurology
The Royal London Hospital
Whitechapel, London E1 1BB

Tel: +44 (0)20 7377 7472
Fax: +44 (0)20 7377 7033
Email: G.Giovannoni@qmul.ac.uk

Gavin Giovannoni MBBCH, PhD, FCP (SA), FRCP, FRCPath
Neuroscience Centre Lead & Professor of Neurology

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* * * * * * * * * * *

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

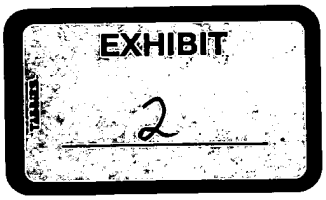
DECLARATION

I, Gavin Giovannoni, declare and state that:

1. I am a Professor of Neurology at the Blizard Institute of Cell and Molecular Science, associated with Barts and The London School of Medicine and Dentistry, located in London, England.

2. I specialize in the study of multiple sclerosis (MS) and other inflammatory disorders of the central nervous system. I am interested in clinical issues related to optimizing MS disease modifying therapies. In one aspect, my research focuses on Epstein Barr virus as a possible cause of MS, MS related neurodegeneration, MS biomarker discovery, MS clinical outcome measures, MS clinical trials and immune tolerance strategy.

3. I have reviewed Lunardi *et al.*, Neurology, Vol. 48(6), 1997, pp1714-1717, and the Bountra *et al.* patent application (WO0061231) (Bountra).



Barts and The London
School of Medicine and Dentistry

Institute of Cell and Molecular Science
Neuroscience Centre
Barts and The London School of Medicine and Dentistry

Postal Address: Department of Neurology
The Royal London Hospital
Whitechapel, London E1 1BB

Tel: +44 (0)20 7377 7472
Fax: +44 (0)20 7377 7033
Email: G.Giovannoni@qmul.ac.uk

Gavin Giovannoni MBBCH, PhD, FCP (SA), FRCP, FRCPath
Neuroscience Centre Lead & Professor of Neurology

4. Prior to the present invention, the recommended daily maximum dosage of lamotrigine (LTG) in the treatment of MS was 400mg daily.

5. Lunardi and colleagues treated 15 patients with trigeminal pain with LTG of which 5 patients had MS (patients 16-20). Of the five patients with MS, the highest dose used was 200mg/day (patient 17).

6. I understand that the assertion is made that a physician treating MS patients would have taken at face value the statement at page 10, lines 3-7 of Bountra, in regard to dosage levels of LTG, that:

> "A suitable dose is for example 0.1 mg/kg to 30 mg/kg body weight per day calculated as the free base, for example 3 mg/kg to 15 mg/kg. A suitable dose for an adult human is for example in the range of 200mg to 900 mg per day."

7. In response, it is my opinion that, at the time of the present invention, an experienced neurologist in this art such as myself would not have contemplated administering LTG to a patient suffering from MS in dosage levels higher than the recommended maximum of 400mg daily. My reasoning is as follows.

8. LTG is neuroprotective in animal models of global and focal ischaemia *in vivo* at doses of 20mg/kg and above, i.e., greater than 4X the anticonvulsant dose in rats (although the ED50 is 2mg/kg, the rat anticonvulsant ED95 is approximately 5mg/kg – for a further discussion on anticonvulsant doses and neuroprotective doses of LTG, see: *The Mechanisms of Action of Lamotrigine,* Meldrum and Leach, 1994, Rev. Contemp. Pharmacother. 5:107-114).

9. In rat middle cerebral artery occlusion (MCAO) model studies published by Smith and Meldrum in 1995 (*Cerebral protective effect of lamotrigine after focal ischemia in rats,* 1995, Stroke:26,117-122), LTG is only neuroprotective in this model of focal ischemia over a narrow

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Institute of Cell and Molecular Science
Neuroscience Centre
Barts and The London School of Medicine and Dentistry

Postal Address: Department of Neurology
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Whitechapel, London E1 1BB

Tel: +44 (0)20 7377 7472
Fax: +44 (0)20 7377 7033
Email: G.Giovannoni@qmul.ac.uk

Gavin Giovannoni MBBCH, PhD, FCP (SA), FRCP, FRCPath
Neuroscience Centre Lead & Professor of Neurology

dose range. In fact, only a dose of 20mg/kg IV significantly reduced neurological scores. The paper concludes:

> "Lamotrigine exhibits a bell-shaped dose-response curve for cerebroprotective effect after MCA occlusion in rats. The optimally effective dose is 20mg/kg, which is 10 fold the anticonvulsant dose in rats (anticonvulsant ED50 values against maximal electroshock-induced or sound- induced seizures are 2mg/kg)".

10. Doses of LTG (10-50mg/kg) higher than anticonvulsant doses have been used in other studies of global ischemia to achieve neuroprotection in gerbil, rat and pig (see *Lamotrigine: Mechanisms of Action.* Leach, Randall, Stefani and Hainsworth, 2002, In: Antiepileptic Drugs, 5th edition, Eds. Levy, Mattson, Meldrum, Perucca).

11. The minimum effective LTG concentration to block white matter ischaemia *in vitro* is 100μM (*Mechanisms of ischaemic damage to central white matter axons: a quantitative histological analysis using rat optic nerve*, Garthwaite *et al.*, Neuroscience, 1999, 94:1219-1230). A usual adult maintenance dose for LTG monotherapy of 100-200mg daily with plasma concentrations around 2-4μg/ml (8-16μM) is far lower than concentrations of LTG to reduce white matter axonopathy.

12. Doses of LTG lower than 400mg per day have been used to treat central pain in patients with MS. In the paper by Leandri and colleagues (*Lamotrigine in trigeminal neuralgia secondary to multiple sclerosis*, Leandri *et al.*, 2000. iNeurol. 247:556-558), doses of 25mg daily to a maximum of 400mg daily were used.

13. Pain due to trigeminal neuralgia in patients with MS is usually due to an inflammatory plaque in the root entry zone of the trigeminal nerve and is typically responsive to anti-convulsant medications within the recommended dose ranges, including that for LTG (<400mg per day).

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Neuroscience Centre
Barts and The London School of Medicine and Dentistry

Postal Address: Department of Neurology
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Gavin Giovannoni MBBCH, PhD, FCP (SA), FRCP, FRCPath
Neuroscience Centre Lead & Professor of Neurology

14. It is important to note that the indication in this context is for trigeminal neuralgia or pain and **not** neuroprotection, which was not investigated in these studies.

15. Doses that work against central pain syndromes appear to be similar to typical anti-convulsant doses and are typically lower than doses employed for neuroprotection.

16. Given the published facts prior to the present invention and subsequent US 2004 patent filing, it is surprising to me and would not have been obvious to me (or any other neurologist with skill in the art of administering LTG) that doses higher than the recommended maximum of 400mg daily could be effective to modify the course of the progressive pathology of MS to the extent exhibited in the patent application.

I declare that all statements herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Gavin Giovannoni

17 - MAY - 2010

Date